Clinical manifestations of rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, inflammatory disorder of unknown etiology that primarily involves synovial joints. The arthritis is typically symmetrical, and usually leads, if uncontrolled, to destruction of joints due to erosion of cartilage and bone, causing joint deformities. The disease usually progresses from the periphery to more proximal joints and results in significant locomotor disability within 10 to 20 years in patients whose disease does not respond to treatment.

The major clinical features of RA, including the articular manifestations, are reviewed here. The systemic and extraarticular features and the diagnosis and differential diagnosis of RA are discussed in detail separately. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis" and "Diagnosis and differential diagnosis of rheumatoid arthritis".)

INITIAL CLINICAL PRESENTATION

Rheumatoid arthritis (RA) most typically presents as polyarticular disease and with a gradual onset, but some patients can present with acute onset, with intermittent or migratory joint involvement, or with monoarticular disease. (See 'Typical 'classic' RA' below and 'Palindromic rheumatism' below and 'Monoarthritis' below.)

The symptoms of RA can affect patients' capacity to perform the activities of daily living (eg, walking, stairs, dressing, use of a toilet, getting up from a chair, opening jars, doors, typing) and those required in their occupation.

Systemic symptoms may also be present in these patients, particularly those with disease onset after age 60 (historically termed "elderly-onset RA"); in up to one-third of patients, the acute onset of polyarthritis is associated with prominent myalgia, fatigue, low-grade fever, weight loss, and depression. Less often, extraarticular manifestations such as nodules or episcleritis may also be present. (See 'Extraarticular involvement' below.)

Articular disease

Typical 'classic' RA — The disease onset in RA is usually insidious, with the predominant symptoms being pain, stiffness (especially morning stiffness), and swelling of many joints [1]. Typically, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the fingers, the interphalangeal joints of the thumbs, the wrists, and the metatarsophalangeal (MTP) joints of the toes are sites of arthritis early in the disease. Other synovial joints of the upper and lower limbs, such as the elbows, shoulders, ankles, and knees, are also commonly affected [2,3].

Morning stiffness is a common feature of those with active RA; it can be defined as "slowness or difficulty moving the joints when getting out of bed or after staying in one position too long, which involves both sides of the body and gets better with movement" [4]. Morning stiffness lasting more than one hour reflects a severity of joint inflammation that rarely occurs outside of active inflammatory arthritis. Morning stiffness, or stiffness after any prolonged period of inactivity (“gelling phenomenon”), is seen in virtually all inflammatory arthropathies [5].

Occasionally, features suggesting polymyalgia rheumatica (PMR) may be present in addition to features of polyarticular RA, and some patients who subsequently develop RA may present with typical PMR. When this occurs in the absence of clinically detectable synovitis, the distinctive clinical features of RA may not develop until months or even years later. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica", section on 'Clinical features' and "Clinical manifestations and diagnosis of polymyalgia rheumatica", section on 'Differential diagnosis'.)

Palindromic rheumatism — The onset of RA is episodic in a few patients, with one to several joint areas being affected sequentially for hours to days, alternating with symptom-free periods that may last from days to months; this episodic pattern is referred to as "palindromic rheumatism." Patients with palindromic rheumatism have similar predisposing genetic risk factors to patients with a more typical persistent presentation of RA and exhibit a similar dose effect of carriage of certain human leukocyte antigen (HLA) alleles [6]. (See "Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis", section on 'Familial and genetic risk factors'.)

The proportion of patients presenting with palindromic rheumatism who progress to develop RA or another well-defined disease varies between studies. In one study of 60 patients with palindromic rheumatism followed over 20 years, 40 (67 percent) developed RA [7]. In another study, among 147 such patients seen in a tertiary referral center, 41 were eventually diagnosed with RA (28 percent) and four with other disorders (three with systemic lupus erythematosus and one with Behçet syndrome) [6].

The presence of anti-citrullinated peptide/protein antibodies (ACPA), a serologic finding that is common in RA, might predict progression of palindromic rheumatism to RA, but evidence evaluating this possibility has been mixed [8]. In one study, involving 61 patients followed for a mean of five-and-a-half years, ACPA testing was performed within a year of symptom onset and antibodies were present in 83 percent of patients who progressed to definite RA, but only 19 percent of those whose disease did not [9,10]. However, in another study, a majority of those with palindromic rheumatism also had ACPA, but there was no significant difference in the frequency of ACPA between patients with persistent palindromic rheumatism and those who subsequently developed RA [11]. (See "Biologic markers in the assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

A response among patients with palindromic rheumatism to hydroxychloroquine, which is also used for the treatment of RA, further supports the possibility that palindromic rheumatism can be a presenting feature of RA. The use of hydroxychloroquine in such patients may also reduce the risk of progression to RA. One retrospective study of 113 patients with palindromic rheumatism found that those who received hydroxychloroquine were 20 percent less likely to develop a chronic rheumatic disease [12].

Monoarthritis — Persistent single joint arthritis (monoarthritis), frequently of a large joint such as the wrist, knee, shoulder, hip, or ankle, may be the sole manifestation of RA or may herald the onset of polyarticular disease. There may be a history of joint trauma as an apparent initiating event. The interval between monoarthritis and polyarthritis may extend from days to several weeks in patients whose disease progresses. Until polyarthritis develops, the approach to such patients is that for any patient with monoarticular arthritis. (See "Monoarthritis in adults: Etiology and evaluation".)

Extraarticular involvement — A proportion of patients complain of a constellation of persistent extraarticular symptoms, which may antedate the onset of polyarthritis by many months; these include generalized aching, stiffness, symptoms of bilateral carpal tunnel syndrome, loss of weight, depression, and fatigue (the last simulating chronic fatigue syndrome [CFS], also known as myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]).

Involvement of the musculoskeletal system other than joints (eg, bone and muscle) and of extraarticular organs (eg, skin, eyes, lungs, heart, and others) occurs in approximately 40 percent of patients with rheumatoid arthritis (RA) over the course of the disease. In addition, patients may rarely present with extraarticular disease in the absence of clinical arthritis.

The systemic and extraarticular manifestations of RA are discussed in detail separately. (See 'Symptoms and physical findings' below and "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)

SYMPTOMS AND PHYSICAL FINDINGS

Joint pain and swelling, especially of the small joints of the hands, wrist, and forefoot are common, along with morning stiffness and decreased grip strength, although all peripheral joints and, to a lesser degree, the more proximal joints of the extremities can be affected. The axial skeleton is usually spared, other than the cervical spine (particularly C1 to C2), where severe disease may cause serious neurologic compromise, generally in patients with longstanding disease. Patients with poorly controlled disease typically experience progressive joint damage, which may result in significant joint deformities and functional impairment (see 'Physical findings of joint inflammation' below and 'Distribution of involved joints' below and 'Upper extremity' below and 'Lower extremity' below and 'Axial skeleton' below and 'Cricoarytenoid joint' below). Disease outcome and functional impairment in rheumatoid arthritis (RA) are reviewed in detail separately. (See "Disease outcome and functional capacity in rheumatoid arthritis".)

Symptoms and findings of systemic and extraarticular manifestations may include generalized aching, stiffness, weight loss, depression, and fatigue. Most patients with extraarticular features of RA have longstanding and severe disease; these features, which are discussed in more detail separately, include anemia, fatigue, subcutaneous ("rheumatoid") nodules, pleuropericarditis, airway and parenchymal lung diseases, neuropathy, episcleritis, scleritis, splenomegaly, Sjögren's disease, vasculitis, and others. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)

Physical findings of joint inflammation — The key features of early rheumatoid inflammation are pain and swelling of the affected joints. Painful inflammation is demonstrated either by local tenderness from pressure applied on the joint or by pain on moving the joint. Swelling may be due to synovial hypertrophy or effusion. Synovial thickening is detected by a "boggy" feel to a swollen joint, and effusion by demonstrating fluctuance. Heat and redness are not prominent features of RA, although an involved joint is often perceptibly warmer on careful examination.

Synovitis of the wrist may present as carpal tunnel syndrome even in very early disease when swelling may not be particularly evident. The characteristic joint deformities are late manifestations of disease that result from the physical stresses and damage to the local anatomy of involved joints.

Distribution of involved joints — RA eventually affects the peripheral joints in almost all patients. Involvement of axial and central joints is less common, occurring in 20 to 50 percent of patients; such joints include the interfacetal and atlantoaxial joints of the neck; the acromioclavicular [13], sternoclavicular, temporomandibular, and cricoarytenoid joints; and the shoulders and hips. Lumbar spine facet joint synovitis may occur, but the frequency of such involvement is rare.

Symmetrical involvement of joints is a characteristic feature, although this may be less apparent early in the disease. The severity of joint disease and consequent deformity is sometimes notably asymmetrical, an observation that may be attributed to increased structural damage to joints related to unilateral overuse of a dominant limb, or joint protection of a limb resulting from neurologic disease. Squeeze tenderness at the metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints and palpable synovial thickening at these joints are characteristic of RA.

Upper extremity

Hands — The main signs of disease can often be found in the hands early in the course of RA [14]. Symmetrical effusions and soft tissue swelling around the MCP and proximal interphalangeal (PIP) joints typically occur. These joints are tender to the touch and exhibit a restricted range of movement (eg, inability to make a fist). Reduced grip strength is a sensitive but nonspecific feature of disease activity affecting the hands and wrists. Palmar erythema may be present (as with any peripheral arthritis).

Occasionally, thickening of the flexor tendons can be detected by palpation of the palm; this finding is due to synovitis of the tendon sheaths ("tenosynovitis"). Nodules may form along the palmar tendon sheaths, resulting in the tendon sheath catching (or triggering) and in an inability to fully extend the finger. The nodules may cause tendon rupture, especially of the extensor pollicis longus (extensor of the distal interphalangeal [DIP] joint of the thumb).

Other physical signs include:

- Reduced grip strength, which is common, can be a surprisingly sensitive indicator of early disease, as well as a useful parameter in the evaluation of disease activity and progression. However, the multiplicity of factors (joint pain, tendon involvement, nerve compression,

and muscle wasting) that contribute to a weak grip makes this assessment rather nonspecific.

- The whole hand may be swollen in very acute RA, with pitting edema over the dorsum giving rise to the "boxing glove" appearance. The range of movement of involved joints is restricted, and loss of active flexion may be so severe that the patient is unable to oppose the fingertips to the palm.

- Between 1 and 5 percent of patients present with carpal tunnel syndrome. Affected patients develop dysesthesia and muscle weakness of the first three fingers and the radial side of the fourth finger. A positive Tinel's or Phalen's sign is usually present. (See "Carpal tunnel syndrome: Clinical manifestations and diagnosis".)

The characteristic joint deformities appear in more established chronic RA. These findings include MCP subluxation, ulnar deviation or "ulnar drift", swan neck and Boutonniere deformities of the fingers (picture 1A-C), and the "bow string" sign (prominence of the tendons in the extensor compartment of the hand). Occasionally, patients present with extensor tendon rupture, most commonly affecting the thumb or little or ring fingers of either hand. The nails and fingertips may show evidence of digital infarcts in patients with rheumatoid vasculitis. (See "Clinical manifestations and diagnosis of rheumatoid vasculitis", section on 'Cutaneous vasculitis'.)

Wrists, elbows, and shoulders — All of the upper extremity joints may be involved in RA, including the wrists, elbows, and shoulders. Wrist involvement is often seen early in the disease course.

- **Wrists** – The wrist is probably the most common upper extremity joint to be involved other than the small joints in the hand. Early in the disease there is a loss of extension. Late changes due to erosive damage lead to volar subluxation and radial drift of the carpus, resulting in increasing prominence of the ulnar styloid and lateral deviation [15]. Tendon rupture can also occur at the wrist.

- **Elbows** – The elbow is frequently affected, with loss of extension (fixed flexion) both in early and late disease (image 1). An effusion or synovitis may be detected as a bulge between the head of the radius and the olecranon. A compressive neuropathy of the ulnar nerve, with dysesthesias of the fourth and fifth fingers, can result from elbow synovitis. Olecranon bursitis is also common. Destruction of the joint may occur due to erosion of cartilage and bone.

The extensor surface of the elbow is the most common site for subcutaneous rheumatoid nodules (picture 2). These should always be visually examined and palpated for in view of their diagnostic and prognostic importance. (See "Rheumatoid nodules".)

- **Shoulders** – The shoulder, being more proximal, tends to be involved later in the disease. A prospective study performed prior to the widespread availability of biologic agents assessed shoulder involvement over time in 74 patients with RA [16]. At 15 years, 55 percent had developed radiographic evidence of erosive glenohumeral joint disease [16]. The most common site for erosions was the superolateral aspect of the humerus.

  Disease in the glenohumeral joint leads to painful restriction of movement resembling a capsulitis, and can result in the development of a "frozen" shoulder. This will typically cause pain at night, when the patient lies on the affected shoulder and marked restriction of range of motion due to the accompanying pain. Rotator cuff injury is common. Effusions are relatively rare, but when they occur, they may be detected in the anterior glenohumeral joint as a filling of the depression under the clavicle anterior to the head of the humerus.

Lower extremity — Lower extremity joints are often involved in RA, particularly in the forefoot and ankles; the knees and hips may also be affected, but hip involvement tends to occur in more severe or longstanding disease. Synovitis in the knee may predispose to the development of popliteal (Baker's) cysts.

- **Feet and ankles** – Foot involvement, especially of the MTP joints, is common in early disease, with a pattern that mirrors that occurring in the hand. Involvement of the feet is typically under-recognized, making it imperative for the clinician to closely inspect the bare feet.

  - Tenderness of the MTP joints may be marked, resulting in the tendency to bear weight on the heels and hyperextend the toes. The fifth MTP is the most frequently involved, and swelling of this joint may be most readily appreciated on examination.

  - Erosive damage results in lateral drift of the toes and plantar subluxation of the metatarsal heads (picture 3), resulting in "cock-up" deformities. The latter may be palpable as bony lumps on the sole with associated callosities.

  - Involvement of the tarsus and the associated tendon sheaths is also common, leading to pain on inversion or eversion of the foot and diffuse edema and erythema over the dorsum of the foot.

- Heel pain may be associated with retrocalcaneal bursitis or tarsal tunnel syndrome, caused by impingement of the posterior tibial nerve. Tarsal tunnel syndrome is also associated with paresthesia of the toes and is important because it can be diagnosed by ultrasound and treated by local injection or surgical release. (See "Overview of lower extremity peripheral nerve syndromes", section on 'Tarsal tunnel syndrome'.)

- Arthritis of the ankle can lead to a diffuse swelling around the tibiotalar joints, which may be red and edematous. These findings may be wrongly attributed to fluid retention or an infective cellulitis of the skin.

- **Knees** – The knee manifests many changes in RA. Synovial thickening is easily detected at the knee, extending the suprapatellar recess around the patella. Effusion is a common feature of knee involvement and can be elicited by patellar tap. Restriction of movement, particularly flexion, is also a common physical finding. If knee synovitis is not controlled, ligamentous laxity leading to deformities and quadriceps atrophy may occur. Erosion of the femoral condyles and tibial plateau can result in either genu varus or genu valgus.

  Patients with RA may develop popliteal (Baker's) cysts, which can be detected by inspection and palpation of the popliteal fossa [17]. Ruptured Baker's cysts extending down the calf are of clinical importance because they can resemble a deep vein thrombosis or acute thrombophlebitis [18]. A history of arthritis, morning stiffness, lack of a palpable occluded venous cord, and edema below the posterior of the knee all suggest a Baker's cyst. Ultrasonography is generally used for the detection of intact or ruptured Baker's cysts (image 2A-B), and they can be readily imaged by magnetic resonance imaging (MRI), although historically a ruptured Baker's cyst was usually demonstrated using arthrography (picture 4) [19]. (See "Popliteal (Baker's) cyst".)

- **Hips** – Involvement of the hips typically occurs only in well-established disease. Hip disease is most frequently manifested as pain in the groin, thigh, or low back, or referred to the knee on standing or movement. Restriction of movement, detected by "log rolling the leg" or rotation of the hip, also may be seen. Pain in the lateral thigh suggests trochanteric bursitis. (See "Greater trochanteric pain syndrome (formerly trochanteric bursitis)".)

Axial skeleton — Cervical spine involvement is relatively common in RA, especially in longstanding disease, compared with the very infrequent involvement that occurs in the thoracolumbar spine or sacroiliac joints. Symptoms of pain and stiffness in the neck are the most typical manifestation, but disease affecting the joints of the cervical spine can be of critical clinical importance, as longstanding disease may lead to instability and cause symptoms related

to subluxation such as neck pain, stiffness, and radicular pain. If the subluxation is causing spinal cord compression, there may be signs of long tract involvement such as hyperreflexia or up going toes on Babinski testing. The clinical manifestations of cervical spine subluxation and the approach to diagnosis and management are discussed in detail separately. (See "Cervical subluxation in rheumatoid arthritis".)

Involvement of the facet joints of the lumbar spine and occasionally discitis has been reported to occur in RA, both from radiographic and post-mortem studies [20]. However, in clinical practice, it is important to exclude more common and serious causes of back pain, such as vertebral compression fractures associated with low bone mass, before attributing back pain to rheumatoid involvement of the lumbar spine.

Cricoarytenoid joint — Approximately 30 percent of patients with RA have involvement of the cricoarytenoid joint demonstrated by indirect laryngoscopy, with the prevalence increasing when advanced imaging techniques are used. As an example, one study from 1984, involving 45 patients with RA, found laryngeal involvement in 32 percent by laryngoscopy and 54 percent by computed tomography (CT) [21]; symptoms may include hoarseness and an inspiratory stridor.

LABORATORY FINDINGS

A number of abnormalities are present in the blood and synovial fluid of patients with rheumatoid arthritis (RA) that reflect the presence of systemic and intraarticular inflammation and the autoimmune features of the disorder; these include inflammatory joint fluid, anemia of chronic inflammation, the presence of rheumatoid factor (RF) and anti-citrullinated peptide/protein antibodies (ACPA), and evidence of an acute phase response that tends to correlate with the degree of disease activity.

- **Synovial fluid** – Synovial fluid examination in affected joints usually reveals an inflammatory effusion, with a leukocyte count typically between 1500 and 25,000/cubic mm characterized by a predominance of polymorphonuclear cells [22]. Cell counts in excess of 25,000 may occur in very active disease, but levels over 25,000 should alert the clinician to the increased possibility of coexisting infection [23,24]. Additional findings in RA synovial fluid are low C3 and C4 complement levels in contrast to higher levels found in the blood. Historically, synovial fluid glucose levels in RA have been noted to be low relative to simultaneous blood glucose measurement, but such testing is not useful in clinical practice. (See "Synovial fluid analysis" and "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Evaluation and diagnosis'.)

- **Hematologic** – Common hematologic abnormalities associated with active disease include anemia of chronic inflammation, thrombocytosis, and sometimes a mild leukocytosis. There is an increased risk of lymphoproliferative disease, including non-Hodgkin lymphoma. Felty syndrome, with neutropenia and splenomegaly, and large granular lymphocyte leukemia are very infrequent. The hematologic features of RA are described in detail separately. (See "Hematologic complications of rheumatoid arthritis" and "Clinical manifestations and diagnosis of Felty syndrome" and "Large granular lymphocyte leukemia in rheumatoid arthritis".)

- **Autoantibodies** – About 75 to 80 percent of patients with RA test positive for RF, ACPA, or both; patients with RA and such antibodies are defined as having "seropositive RA" and the presence of the antibodies has diagnostic, therapeutic, and prognostic implications. About a quarter to a third of patients have antinuclear antibodies as well. Other autoantibody responses to post-translationally modified proteins have been observed in RA, though their clinical utility has not been defined. These serologic features of RA are reviewed in detail separately. (See "Biologic markers in the assessment of rheumatoid arthritis" and "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Evaluation and diagnosis'.)

- **Acute phase response** – Measures of the acute phase response, including the erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP), are usually elevated in patients with active disease, and the degree of elevation in a given patient tends to correlate with disease activity; however, mild disease activity is sometimes present without such abnormalities. ESR and CRP in RA and the acute phase response are discussed in more detail separately. (See "Biologic markers in the assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate' and "Biologic markers in the assessment of rheumatoid arthritis", section on 'C-reactive protein' and "Acute phase reactants".)

IMAGING

Patients with rheumatoid arthritis (RA) develop joint space narrowing and bony erosions, which are typically evaluated using plain radiographs of the hands and feet (see 'Plain film radiography' below). These radiographic changes may already be present when first seen by a clinician but more usually become evident over time with ongoing synovitis beyond the first few months of disease. Erosions of cartilage and bone are among the cardinal features of RA. However, they can also occur in some other forms of inflammatory and gouty arthropathy and are therefore not diagnostic of RA in and of themselves. (See "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Differential diagnosis'.)

MRI studies and ultrasonography are more sensitive than radiography for the detection of changes resulting from synovitis, but additional research is ongoing to determine the prognostic importance of changes observed with these studies that are not evident radiographically. (See 'MRI' below and 'Ultrasonography' below.)

Plain film radiography — Progressive radiographic changes occur in the affected joints of patients with active disease, including periarticular osteopenia, joint space narrowing, and bone erosions. Deformities, including joint subluxation, and secondary degenerative changes may occur with an active disease course.

Plain radiographs are often normal early in disease, and the early changes evident on plain films may include only soft tissue swelling and periarticular osteopenia (image 3A-C). To be detected by plain radiography, erosions must have eroded through the cortex of the bone around the margins of the joint. In studies done in the late 1980s and early 1990s, erosions in the metacarpophalangeal (MCP) (image 4A-B and image 5) and proximal interphalangeal (PIP) joints (image 6A-B) were identified by plain radiography in 15 to 30 percent of patients in the first year of the disease. By the end of the second year of disease in patients who did not respond to therapy, the cumulative incidence of erosions was 90 percent [25,26]. In some patients, erosions occur first in the ulnar styloid (image 7A-B) or metatarsophalangeal (MTP) joints (image 8A-B). Joint space narrowing may also be present. Radiographic evidence of joint injury in patients with early RA is often greater in the dominant than the nondominant hand [27]. Similar asymmetry in joint damage has long been observed in patients with hemiplegia [28].

With extreme destruction, the severity of erosions may reach a level beyond which further progression cannot be assessed radiographically, despite the presence of ongoing joint damage [29].

MRI — MRI is a more sensitive technique than plain radiography for identifying bone erosions; however, the clinical significance of erosions only detected by MRI awaits elucidation [30]. When radiography and MRI were compared in a group of 55 patients with early arthritis, MRI identified seven times as many erosions in the MCP and PIP joints than plain radiography [31].

MRI also may detect bone erosions earlier in the course of the disease than is possible with plain films [32]. As an example, approximately 45 percent of patients with symptoms for only four months were found to have erosions detected by this method [33]. Decreased signal from the bone marrow on T1-weighted images and enhancement of the marrow with gadolinium administration is interpreted as bone marrow edema. The presence of marrow edema on MRI is

predictive of later development of erosive disease [34]. A similarly increased sensitivity of MRI has also been noted for early RA of the forefoot [35].

It is also possible to identify and estimate the quantity of hypertrophic synovial tissue using MRI. The presence of MRI-detected synovial proliferation correlates with the later development of bone erosions [36]. Use of this imaging technique outside of research settings may be hastened by the development of MRI scanners that are designed specifically for imaging the extremities, but clinical indications for the use of such techniques remain uncertain [37,38].

Ultrasonography — Ultrasonography is another sensitive alternative imaging technique for estimating the degree of inflammation and the volume of inflamed tissue. Direct comparison of color Doppler ultrasonography and contrast-enhanced MRI in one study of 29 patients demonstrated agreement regarding the presence or absence of inflammation between the two techniques in 75 percent of the joints of the hands and wrists [39]. Both imaging modalities found features of inflammation in joints that were neither tender nor swollen on physical examination. The clinical importance of these findings remains to be determined. Ultrasonography can also be used to assess the MTP joints, which may become affected early in the course of disease [40]. Ultrasound evaluation for bone erosions and synovitis is described in further detail separately. (See "Musculoskeletal ultrasonography: Clinical applications", section on 'Joints'.)

CLINICAL COURSE

Rheumatoid arthritis (RA) shows a marked variation of clinical expression in individual patients (table 1). These differences may be apparent in the number of involved joints and pattern of joint involvement, fluctuations in disease activity and ability to achieve remission, and the rate of progression and extent of structural damage. Some patients may have mainly small joints or large joints affected. A given patient may also have only a few or almost all joints involved. In addition, extraarticular disease may be prominent in a subset of patients. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)

Patterns of progression — Variation is seen in the course of disease activity and the rapidity of structural damage to joints [41].

- Most patients show fluctuation of disease activity over periods lasting weeks to months. This corresponds to an increase or decrease in symptoms of arthritis, a pattern which may recur throughout the course of the disease.

- The early initiation of disease-modifying antirheumatic drugs (DMARDs) improves the likelihood of attaining clinical remission, although sustained remission occurs in the minority of patients. Drug-free remission, defined as clinical remission without requiring DMARD therapy, is very rare [42,43]. (See 'Remission' below.)

Disease activity versus structural damage — The concept of disease activity is based upon the state of the underlying inflammatory response and may be distinguished from the destructive process that leads to irreversible damage of the joint (table 2):

- Disease activity can (and does) vary. This variation in part reflects the endogenous rhythms of the disease process but is mainly the result of therapeutic interventions. Thus, periods of spontaneous exacerbations and quiescence, characterized by an increase (a "flare") or decrease in symptoms, are modulated by both the beneficial effects of drug therapy and withdrawal of therapy due to loss of efficacy or side effects. The assessment of disease activity in patients with RA is described in detail separately. (See "Assessment of rheumatoid arthritis disease activity and physical function".)

- By contrast, structural damage is cumulative and irreversible. The degree of damage is closely linked to inflammation and hence to disease activity, but is also associated with degeneration and repair [44]. As structural damage progresses, the detection of variation in disease activity by clinical examination becomes increasingly difficult. At these later stages, symptoms and signs of inflammation, such as pain, stiffness, tenderness, swelling, and joint effusions, may be caused either by continuing rheumatoid disease or as a secondary result of mechanical and degenerative change.

Remission — Disease remission occurs when there is little or no evidence of clinical disease activity (see below for criteria). However, achieving remission does not entirely preclude the development of further erosive changes. This was illustrated in a retrospective study of 187 patients who were in remission for six months and whose clinical course and radiographic findings were subsequently followed [45]. A majority (52 percent) remained in remission during two years of follow-up. However, despite inapparent clinically active disease, one new erosion in a previously unaffected joint appeared in 14 percent of these patients.

In our experience, reaching and maintaining remission is very rare without DMARDs. As an example, among 191 patients treated with such drugs beginning within a year of disease onset, 48 (25 percent) met criteria for remission after three years of treatment, and 38 (20 percent) after five years of DMARD therapy [46]. The likelihood of achieving remission with DMARD treatment within the first year of disease was greater in patients with less initial disease activity,

less disability, lower levels of acute phase reactants, absence of rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPA), and less radiographic joint damage.

Attempts to define clinical remission for clinical practice and in clinical trials, in order to understand better the natural history of RA and the effects of therapy, have resulted in provisional definitions of remission by a joint effort of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR; formerly known as European League Against Rheumatism) [47-49]. These definitions take into account that a complete lack of joint pain, swelling, and tenderness may be impossible to achieve in patients who have developed structural damage of the joints or who have other medical conditions, despite actual remission in the rheumatoid disease process. The absence of all such symptoms and findings is not required by the ACR/EULAR criteria, and revised criteria endorse a less stringent patient global assessment cutoff. (See "Assessment of rheumatoid arthritis disease activity and physical function", section on 'Criteria for remission'.)

The ACR/EULAR (2022 revision) definitions of remission include use of the Clinical Disease Activity Index, Simplified Disease Activity Index, or Boolean 2.0 remission (which requires tender joint count swollen joint count, C-reactive protein (in mg/dL) ≤1, and patient global assessment [0-10 scale] ≤2) [49].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Rheumatoid arthritis (The Basics)" and "Patient education: Hand pain (The Basics)")

- Beyond the Basics topics (see "Patient education: Rheumatoid arthritis symptoms and diagnosis (Beyond the Basics)" and "Patient education: Rheumatoid arthritis treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Initial presentation and typical disease course** – The onset of rheumatoid arthritis (RA) is usually insidious, with the predominant symptoms being pain, stiffness, and swelling of many joints. Typically, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the fingers, the interphalangeal joints of the thumbs, the wrists, and the metatarsophalangeal (MTP) joints of the toes are sites of arthritis early in the disease. Other joints of the upper and lower limbs are also commonly affected later in the disease course. Onset may occasionally be intermittent or with migratory joint involvement, or may be monoarticular. RA may adversely affect a patient's capacity to perform the activities of daily living. (See 'Initial clinical presentation' above and 'Typical 'classic' RA' above and 'Palindromic rheumatism' above and 'Monoarthritis' above.)

- **Major symptoms and findings of early disease** – The key features of early rheumatoid inflammation are pain and swelling of the affected joints. Painful inflammation is demonstrated either by local tenderness from pressure applied on the joint or by pain on moving the joint. Swelling may be due to synovial hypertrophy or effusion. Synovial thickening is detected by a "boggy" feel to a swollen joint, and effusion by demonstrating fluctuation. (See 'Symptoms and physical findings' above and 'Hands' above and 'Lower extremity' above and 'Axial skeleton' above and 'Cricoarytenoid joint' above.)

- **Distribution of joint involvement** – RA eventually affects the peripheral joints in almost all patients. Involvement of axial and central joints is less common, occurring in 20 to 50 percent of patients. Symmetrical joint involvement is characteristic, although this may be less apparent early in the disease. The pattern of joint involvement may also be diagnostically useful. Squeeze tenderness at the MCP and metatarsophalangeal MTP joints and palpable synovial thickening at these joints are characteristic of RA. (See 'Distribution of involved joints' above.)

- **Extraarticular features** – Extraarticular features of RA, including anemia, fatigue, subcutaneous ("rheumatoid") nodules, pleuropericarditis, obstructive and parenchymal lung diseases, neuropathy, episcleritis, scleritis, splenomegaly, Sjögren's disease, vasculitis, and kidney disease, may occur during the course of the disease. (See

'Extraarticular involvement' above and "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)

- **Laboratory findings** – A number of abnormalities are present in the blood and synovial fluid of patients with RA. These include changes reflecting systemic and intraarticular inflammation, and the autoimmune features of the disorder, including the presence of rheumatoid factors (RF) and anti-citrullinated protein/peptide antibodies (ACPA). (See 'Laboratory findings' above.)

- **Imaging findings** – Patients with RA develop joint space narrowing and bony erosions, which are often observed in plain radiographs of the hands and feet. These may already be present when first seen by a clinician but more usually become evident over time with ongoing synovitis beyond the first few months of disease. MRI and ultrasound are more sensitive imaging modalities than plain radiographs. (See 'Imaging' above.)

- **Variation in clinical course and pattern of presentation** – RA shows a marked variation of clinical expression in individual patients (table 1). This difference may be apparent in the number and pattern of joint involvement and whether extraarticular disease is prominent. Variation is also seen in the course of disease activity and the rapidity of structural damage to joints. (See 'Clinical course' above and 'Patterns of progression' above.)

- **Disease activity versus structural damage** – The concept of disease activity is based upon the state of the underlying inflammatory response, and may be distinguished from the irreversible damage of the joint that results from this inflammatory response (table 2). In a minority of patients, disease activity is absent; in this circumstance, the disease is said to be in remission, but typically continues to require disease-modifying antirheumatic drug (DMARD) therapy. (See 'Disease activity versus structural damage' above and 'Remission' above.)

ACKNOWLEDGMENTS

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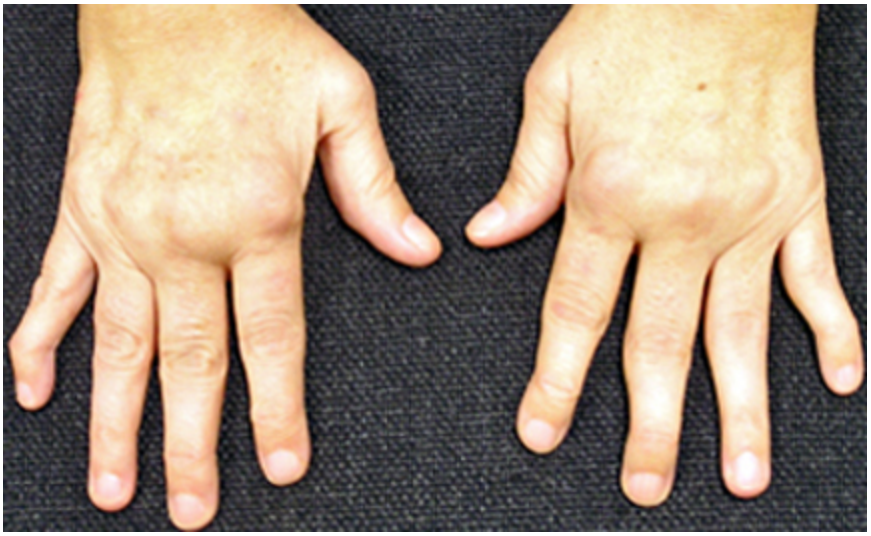
Topic 7502 Version 41.0

GRAPHICS

Synovial thickening of the metacarpophalangeal joint



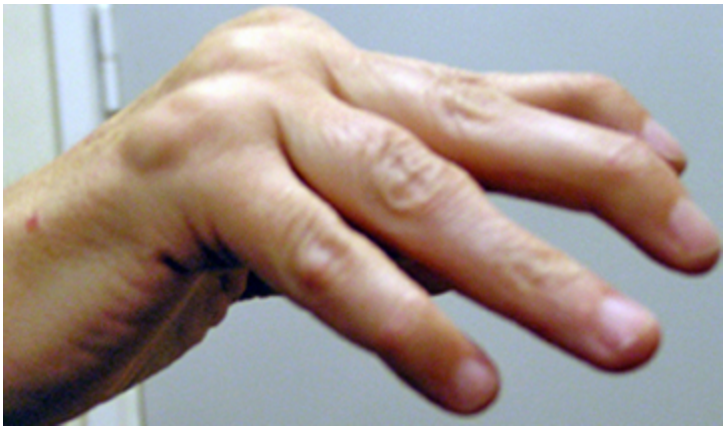
Bilateral swelling of the MCP joints is evident in this patient with rheumatoid arthritis. Note also the mild swan neck deformities present in several fingers, particularly the left middle and fifth fingers.

MCP: metacarpophalangeal.

Courtesy of Patrick J Venables, MD.

Graphic 57439 Version 2.0

Swelling of the metacarpophalangeal joints of the right hand in rheumatoid arthritis



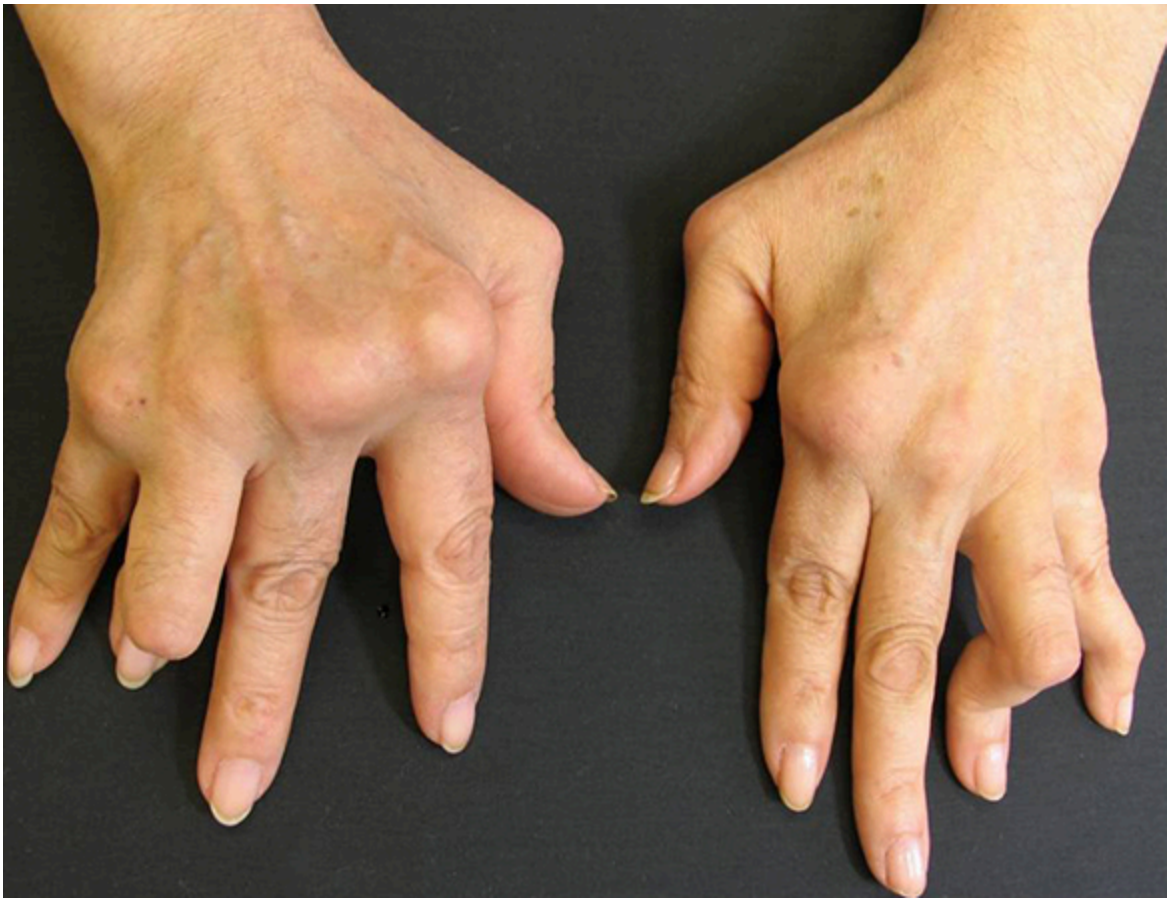
Swelling of the MCP joints, moderate MCP flexion, and swan neck deformities are evident in this patient with rheumatoid arthritis.

MCP: metacarpophalangeal.

Courtesy of Patrick J Venables, MD.

Graphic 66140 Version 3.0

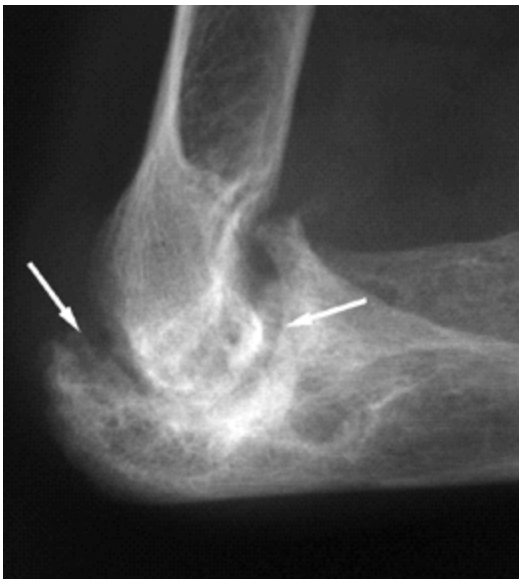
Rheumatoid arthritis hand deformities: Boutonniere deformity and Z-deformit of the thumb



A woman with longstanding rheumatoid arthritis has soft tissue swelling and subluxation of the metacarpophalangeal joints. The right thumb shows hyperextension of the interphalangeal joint (a Z deformity). Both ring fingers have boutonniere deformities with flexion of the proximal and hyperextension of the distal interphalangeal joints.

Graphic 96568 Version 8.0

Rheumatoid arthritis of the elbow

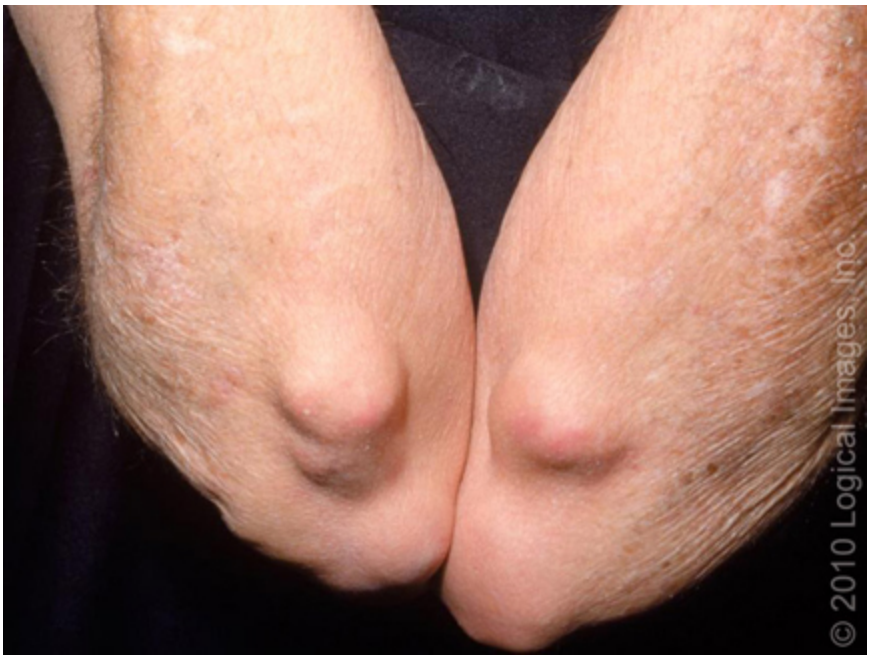


Lateral view of the elbow in a patient with rheumatoid arthritis (RA) reveals soft tissue swelling and osteopenia with destruction of the elbow joint (arrows). There are also secondary proliferative bony changes, which have arisen due to joint space destruction.

Courtesy of Jonathan Kruskal, MD.

Graphic 76905 Version 3.0

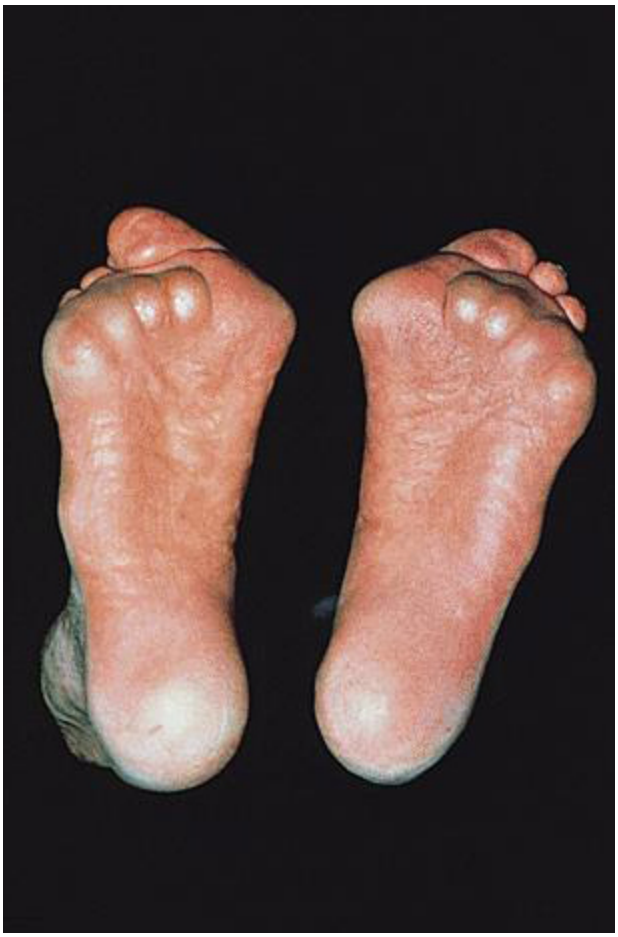
Rheumatoid nodules



Rheumatoid nodules are firm, nontender lesions that typically occur in areas of trauma in individuals with rheumatoid arthritis. Nodules are present near the elbows in this patient.

Graphic 74194 Version 5.0

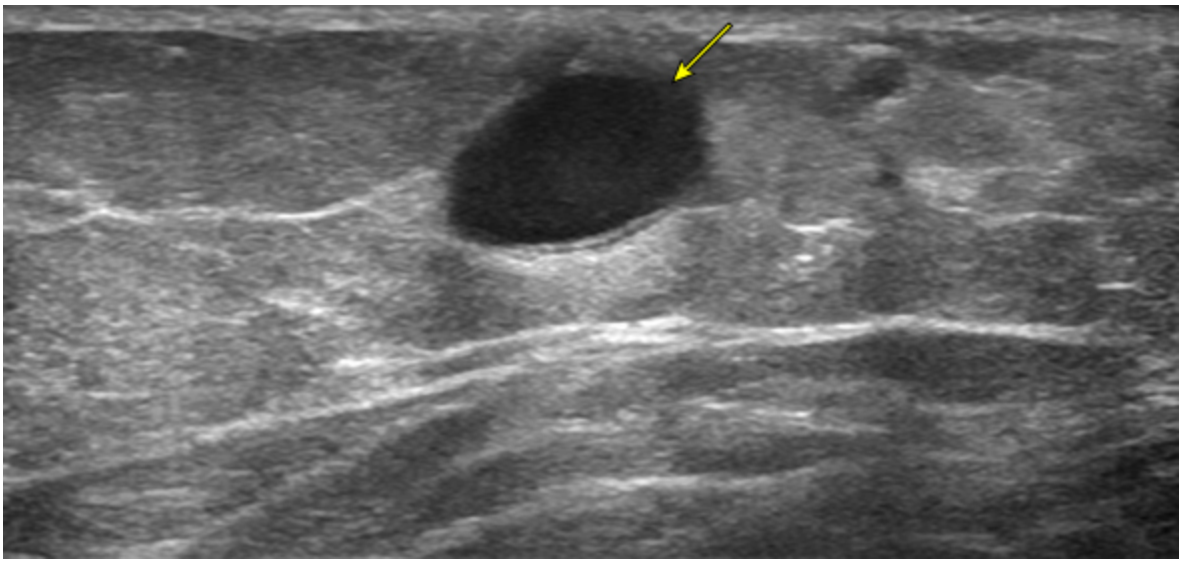
Rheumatoid arthritis in the feet: Metatarsal head subluxation



Chronic inflammation at the metatarsophalangeal (MTP) joints causes damage resulting in subluxation of the toes upwards. With the MTP joints displaced, weightbearing is not shared through the toes, but falls directly on the prominent metatarsal heads. This painful condition results in pain on weightbearing and difficulty in walking, and can cause the metatarsal to erode through the skin on the sole of the foot. Treatment in the early stages includes appropriate shoes and fitting of an orthotic that will support weight away from the painful metatarsal heads. Late-stage treatment may involve surgical excision of the prominent metatarsal heads.

Graphic 96569 Version 9.0

Small popliteal cyst on ultrasound imaging

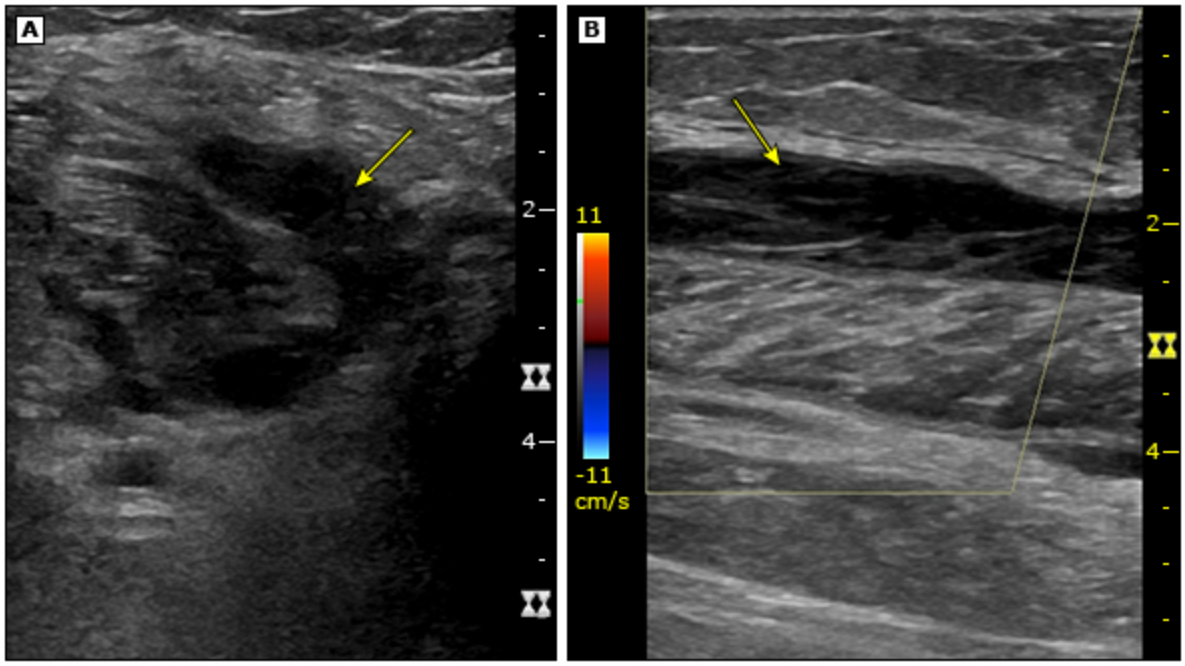


US in transverse projection shows a popliteal cyst (arrow) that measures 1.1 cm by .75 cm.

US: ultrasound.

Graphic 91804 Version 2.0

Ruptured popliteal cyst on ultrasound

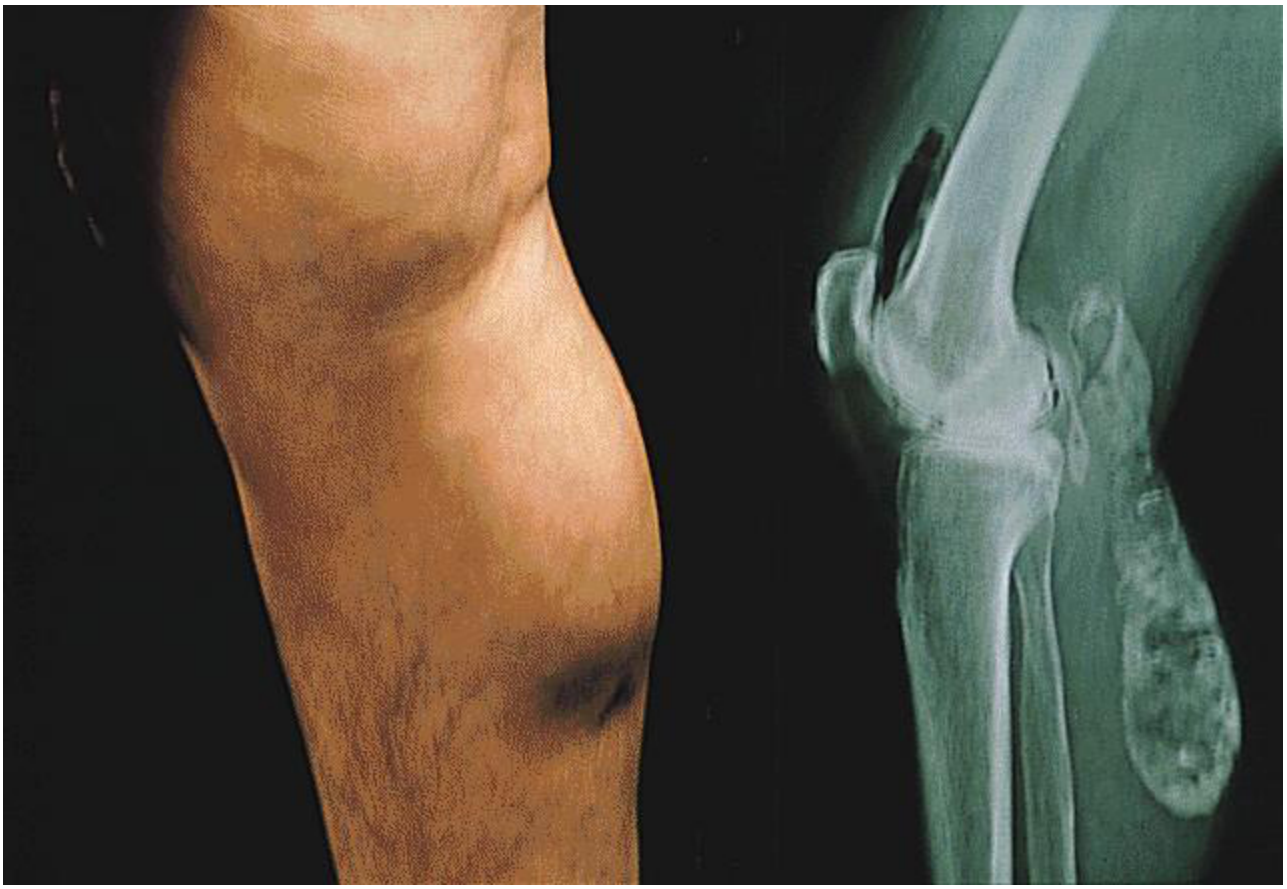


US through the popliteal fossa (A) in transverse projection shows a decompressed popliteal cyst (arrow). Image B is a longitudinal view inferior to the popliteal fossa and shows fluid dissecting through the muscle planes (arrow).

US: ultrasound.

Graphic 91806 Version 2.0

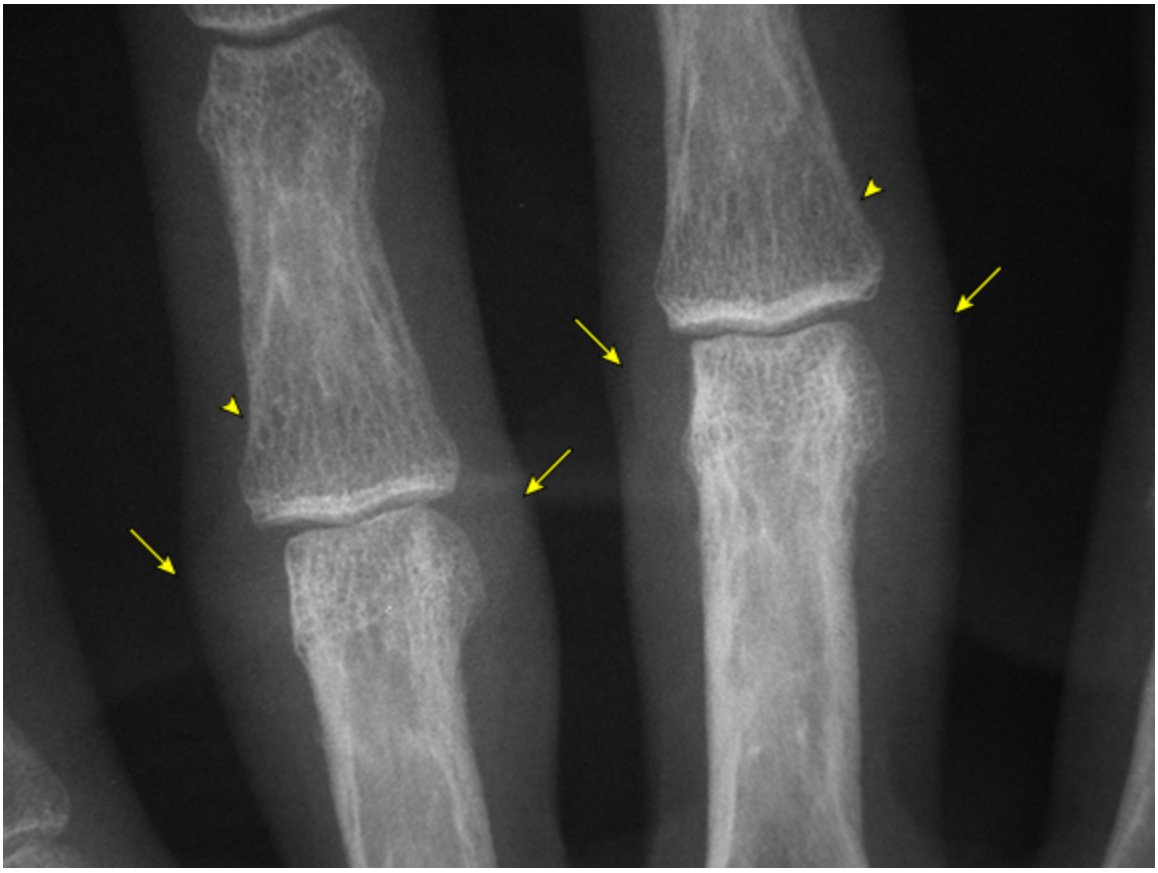
Popliteal (Baker's) cyst, knee (photograph and arthrogram)



A synovial cyst is a soft, fluid-filled mass under the skin that may occur over any synovial joint. It is caused by herniation of synovial tissue, which then fills with fluid. In popliteal, or Baker's, cyst a fluctuant swelling is present in the popliteal area, occasionally extending well into the calf, as shown on the left. An arthrogram of a popliteal cyst in a patient with rheumatoid arthritis is shown on the right. If the cyst ruptures, acute swelling and pain identical to thrombophlebitis may occur. Ultrasound may be done to delineate the problem, and an arthrogram can be used to confirm the diagnosis.

Graphic 131358 Version 5.0

Soft tissue swelling and periarticular osteopenia of proximal interphalangeal joints in rheumatoid arthritis

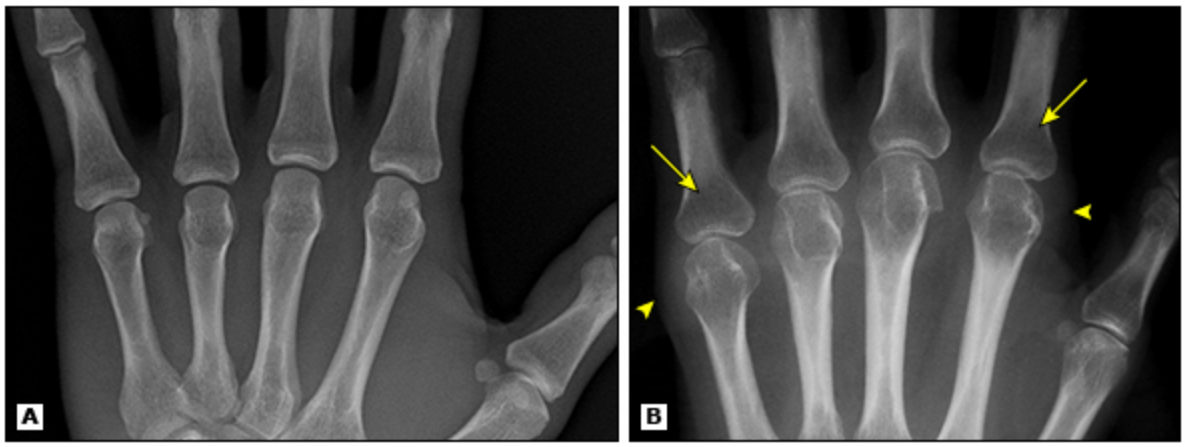


The plain radiographs of the hand are magnified at the proximal interphalangeal joints of the third and fourth fingers showing soft tissue swelling (arrows) and periarticular osteopenia (arrowheads).

Courtesy of Richard Waite, MD.

Graphic 83905 Version 2.0

Plain radiograph of osteopenia of metacarpophalangeal joints in rheumatoid arthritis



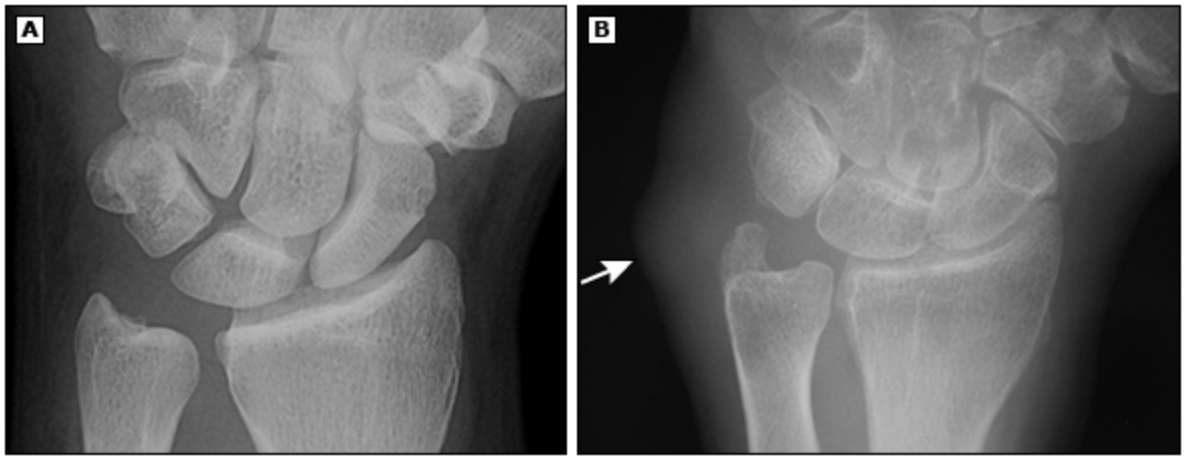
The plain radiograph of the left hand in the AP projection shows a normal patient (A) and a patient with radiologically mild rheumatoid arthritis (B). The patient with rheumatoid arthritis demonstrates osteopenia around the metacarpophalangeal joints (arrows) and mild soft tissue swelling (arrowheads).

AP: anteroposterior.

Image B courtesy of Richard Waite, MD.

Graphic 85825 Version 2.0

Plain radiograph of osteopenia of the wrist in rheumatoid arthritis



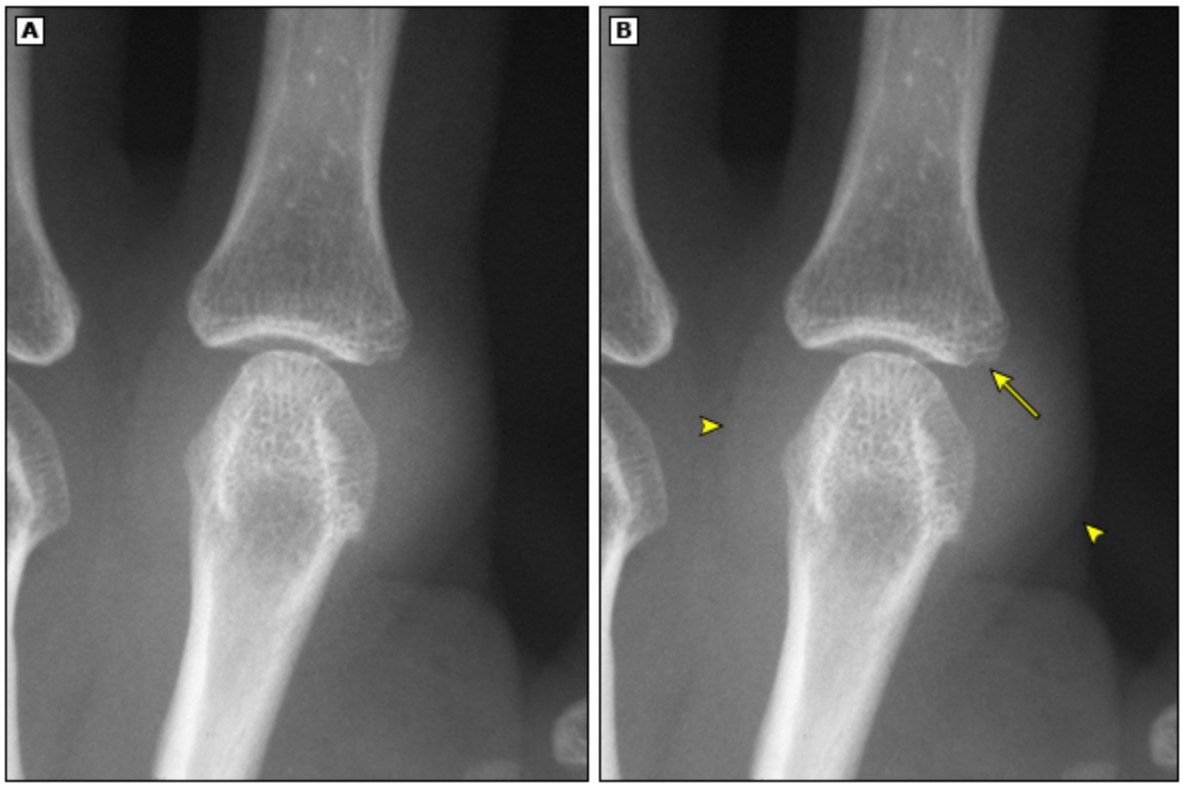
The normal radiograph of the left wrist in the AP projection (A) is compared with the left wrist of a patient with rheumatoid arthritis (B). The subtle diffuse osteopenia of the carpal bones is typified by an overall decrease in the density of the bones and by a relative paucity of trabecular markings. Less subtle is the prominent soft tissue nodule overlying the styloid process (arrow).

AP: anteroposterior.

Image B courtesy of Richard Waite, MD.

Graphic 85829 Version 2.0

Plain radiograph of mild metacarpophalangeal joint erosion rheumatoid arthritis

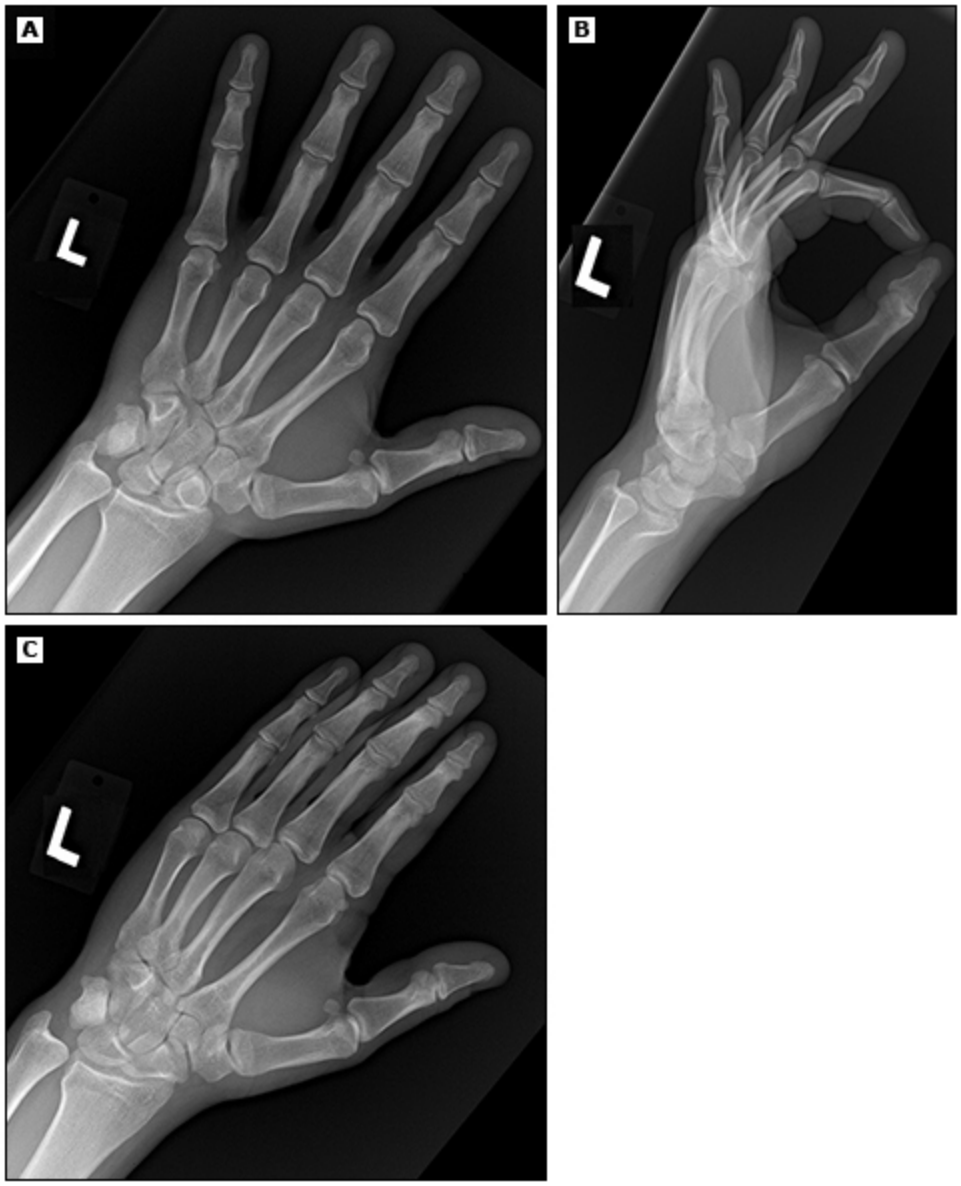


The plain x-ray of the left hand is from a patient with radiologically mild rheumatoid arthritis. The magnified view of the second metacarpophalangeal joint in (A) is shown with arrows in (B). Subtle erosive changes are noted at the second metacarpophalangeal joint (arrow), while soft tissue changes are more obvious (arrowheads).

Courtesy of Richard Waite, MD.

Graphic 85826 Version 3.0

Plain radiograph of normal left hand (AP, lateral, and oblique)

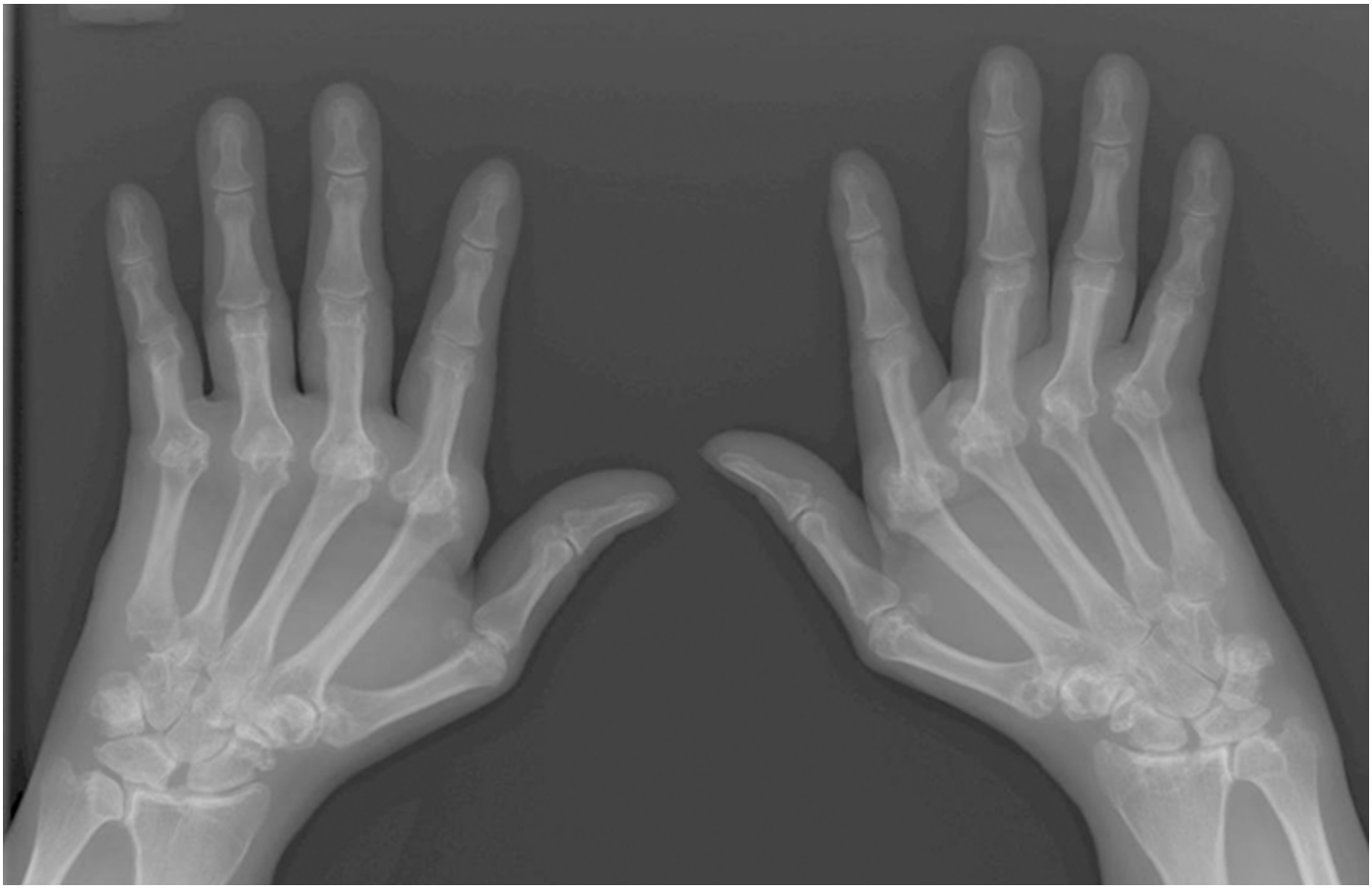


The radiographs of the left hand in the AP (A), lateral (B), and oblique (C) projections are normal.

AP: anteroposterior.

Graphic 85827 Version 2.0

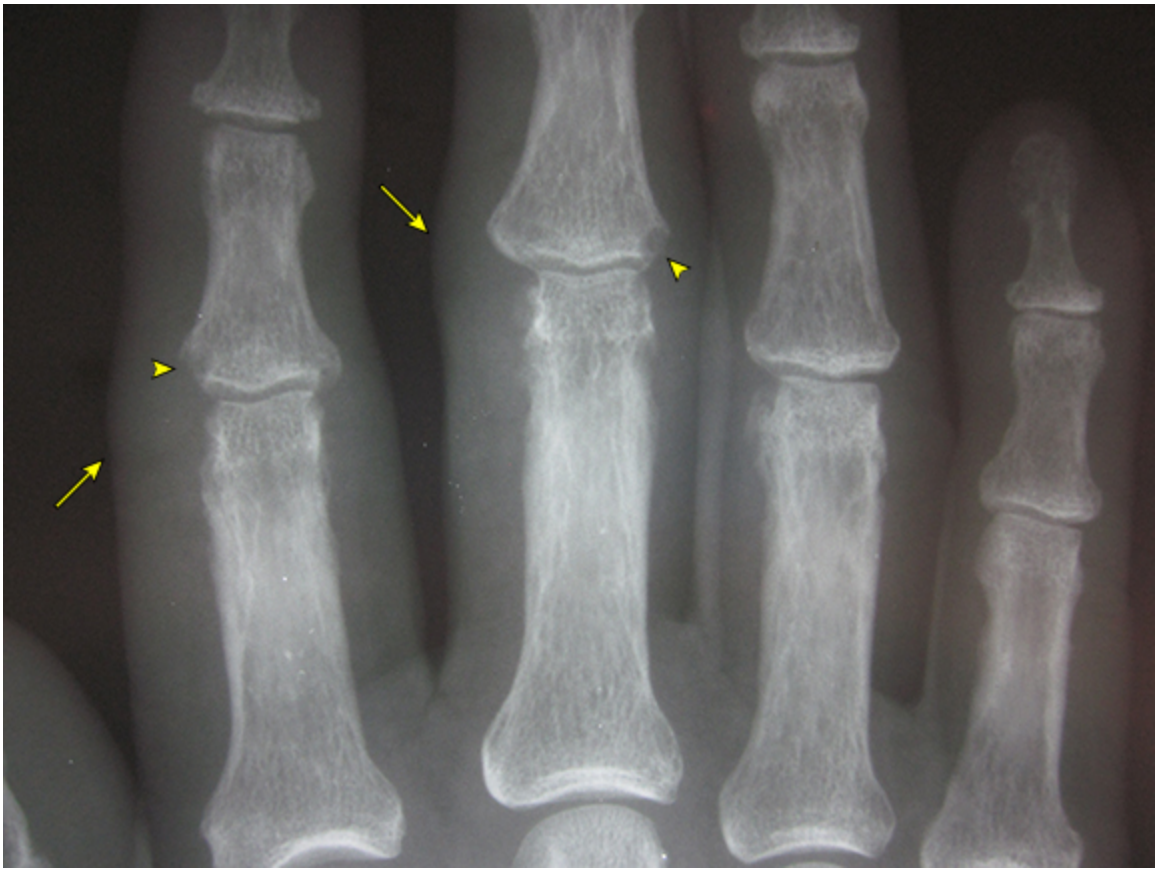
Rheumatoid arthritis: Severe erosive changes and hand deformities (plain radiography)



Erosive changes of the metacarpophalangeal joints with ulnar subluxation are evident.

Graphic 131357 Version 5.0

Plain radiograph of rheumatoid arthritis proximal interphalangeal joint erosions

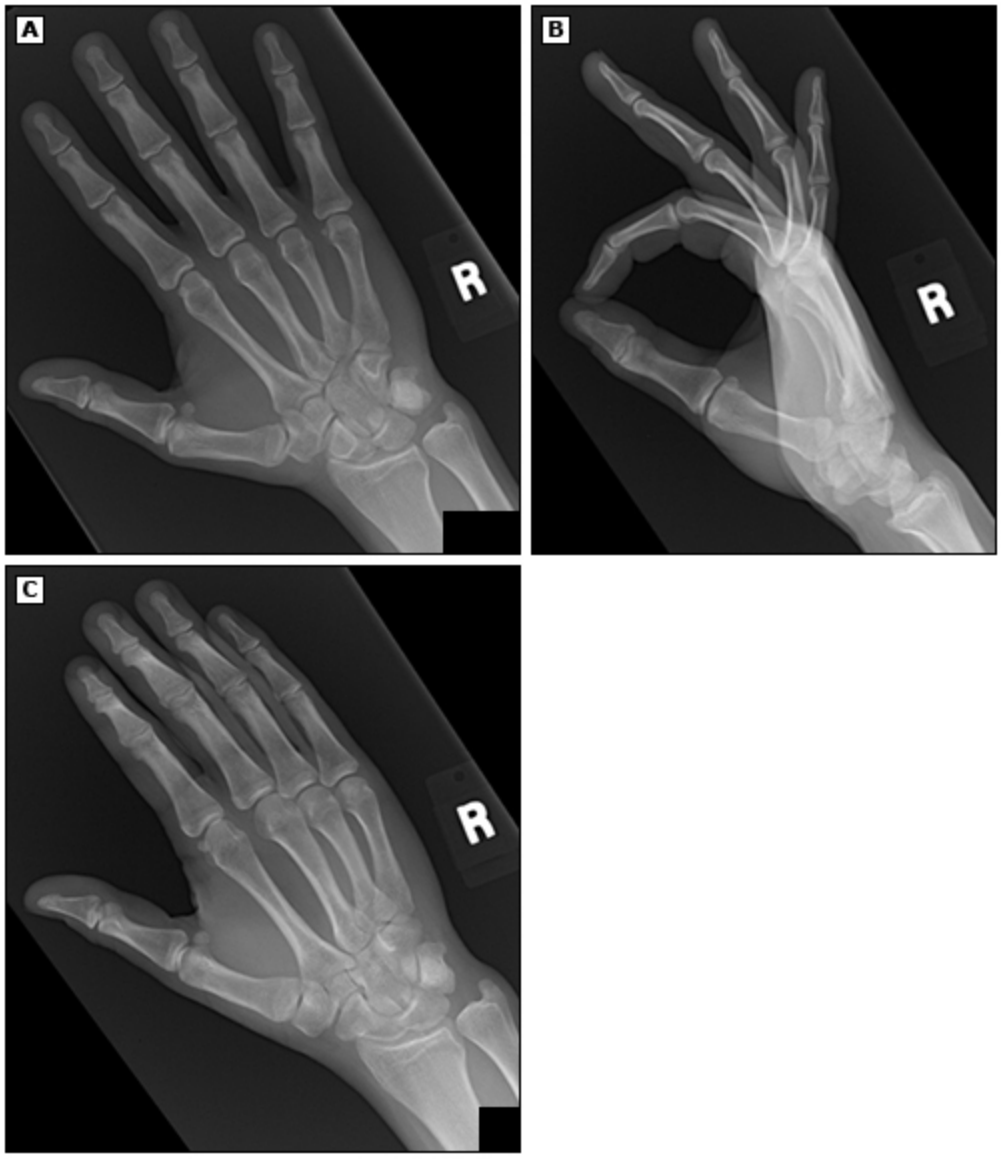


The plain x-ray of the right hand magnified at the proximal interphalangeal joints shows soft tissue swelling (arrows) and mild erosive changes (arrowheads).

Courtesy of Richard Waite, MD.

Graphic 85824 Version 3.0

Plain radiograph of a normal right hand (AP, lateral, and oblique)

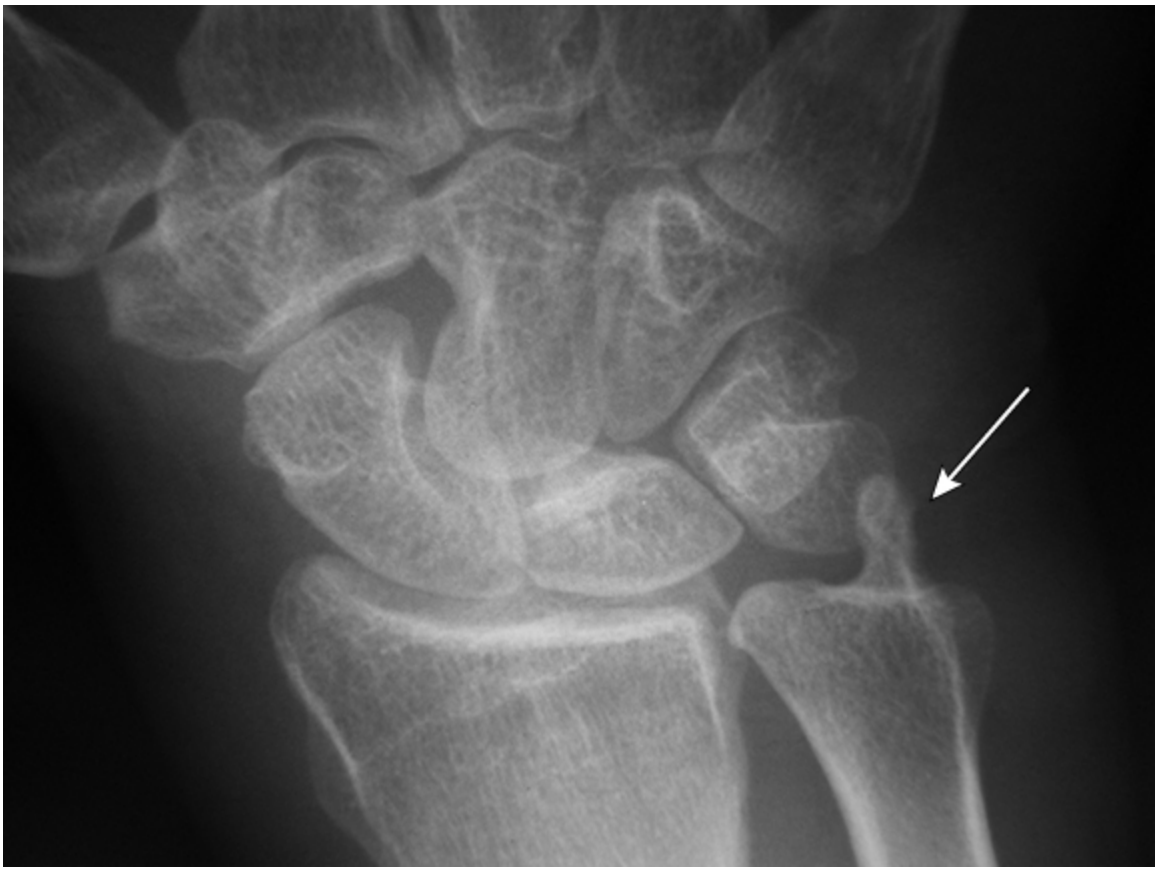


The radiographs of the right hand in the AP (A), lateral (B), and oblique (C) projections are normal.

AP: anteroposterior.

Graphic 85836 Version 4.0

Plain radiograph of ulnar styloid erosion in rheumatoid arthritis



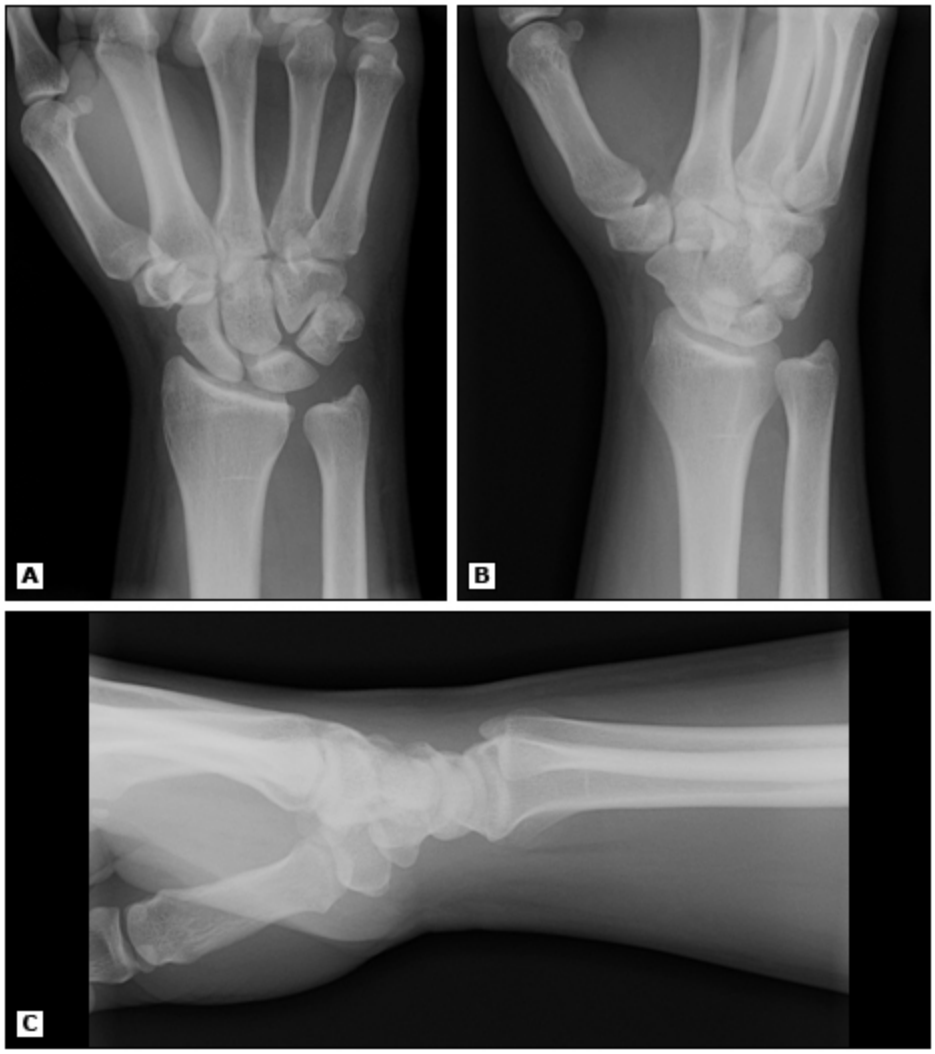
The radiograph of the right wrist in the AP projection reveals a deformed and eroded ulnar styloid process (arrow) in this patient who has rheumatoid arthritis. No other remarkable changes are present.

AP: anteroposterior.

Courtesy of Richard Waite, MD.

Graphic 85828 Version 2.0

Plain radiograph of a normal wrist

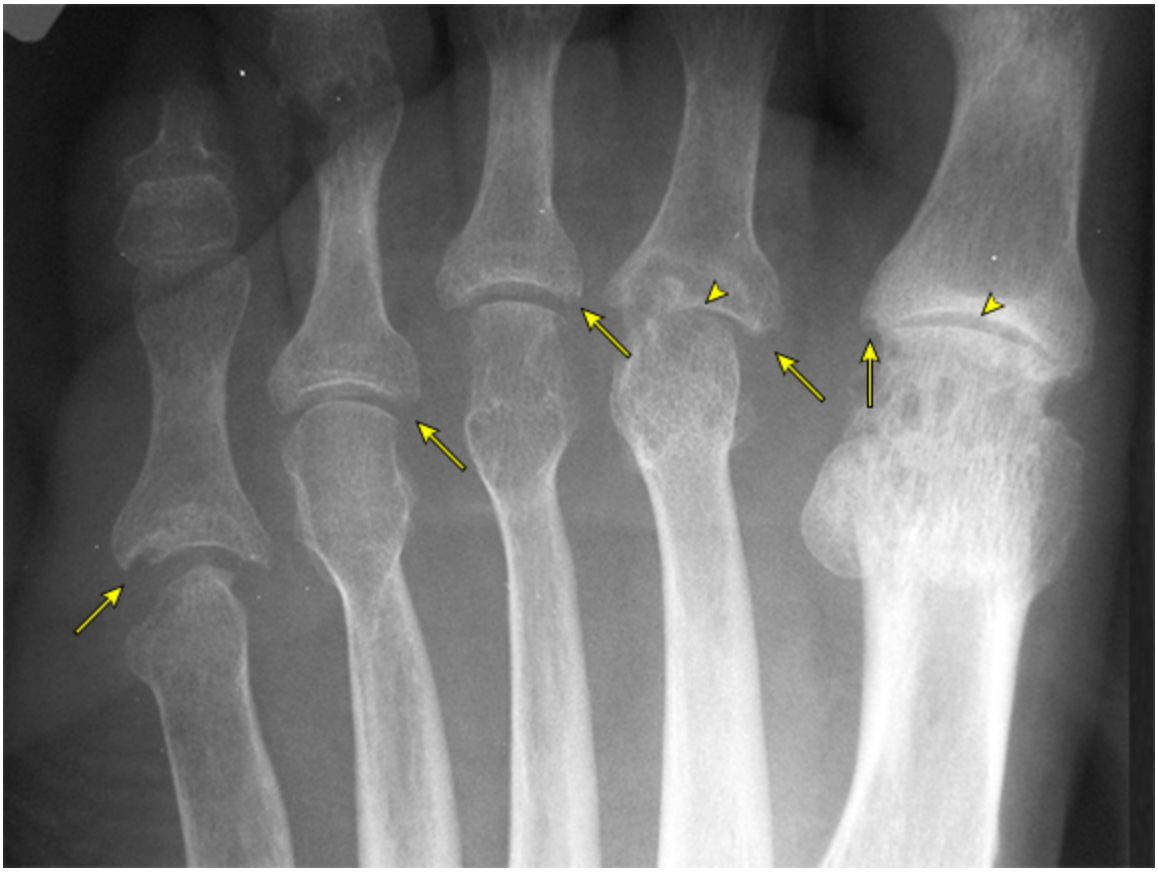


The radiograph of the normal right wrist is displayed in the AP (A), oblique (B), and lateral (C) projections.

AP: anterior posterior.

Graphic 85830 Version 3.0

Plain radiograph of metatarsophalangeal joint space narrowing and erosions i rheumatoid arthritis



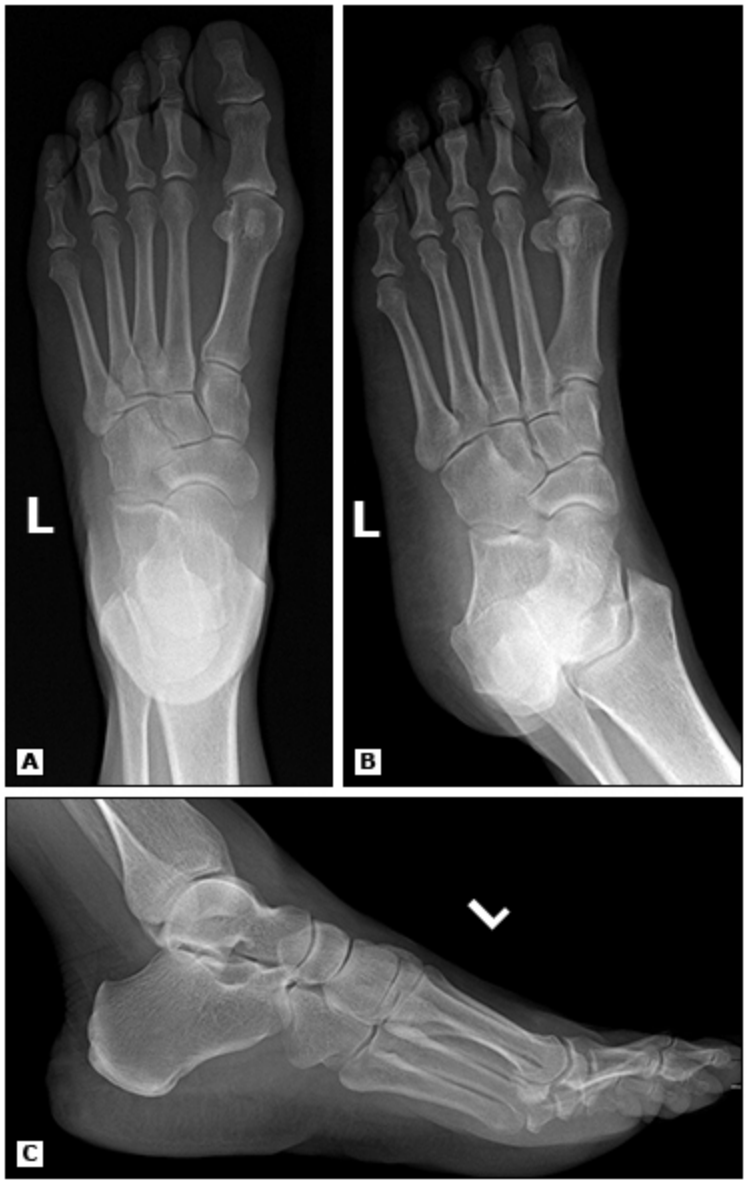
The radiograph of the left foot in the AP projection demonstrates an erosion in the periarticular, marginal "bare" area of the joint of the 5th MTP joint and more subtle erosions at the 1st, 2nd, 3rd, and 4th MTPs (arrows), characteristic of rheumatoid arthritis. Also present is joint space narrowing of the 1st and 2nd MTP joints (arrowheads).

AP: anteroposterior; MTP: metatarsophalangeal.

Courtesy of Richard Waite, MD.

Graphic 85831 Version 2.0

Plain radiograph of normal left foot



The normal radiograph of the left foot is from a 53-year-old female. The foot is shown in the AP (A), oblique (B), and lateral projections (C).

AP: anterior-posterior.

Graphic 85820 Version 2.0

Clinical manifestations of rheumatoid arthritis through the disease course

Joint inflammation and damage:
Synovial proliferation and joint effusion
Marginal joint erosions
Ligamentous laxity and joint deformity
Impaired physical function and quality of life
Indefinite need for DMARDs
Increased risk for development of other diseases
Infections
Cardiovascular disease
Malignancies (lymphoma, lung cancer, skin cancers, among others)
Pulmonary disease
Life expectancy of RA less than age- and sex-matched control populations, especially in patients with:
Polyarticular disease
Systemic extraarticular disease
Persistent disease activity (high ESR, CRP, and clinical disease activity measures)
Rheumatoid factor and circulating immune complex positivity
HLA-DRB1 "shared epitope" (especially biallelic)

DMARDs: disease-modifying antirheumatic drugs; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HLA: human leukocyte antigen.

Graphic 75843 Version 5.0

Assessment of disease activity in rheumatoid arthritis

Symptoms
Duration of morning stiffness
Pain score (visual analogue scale)
Fatigue - severity (visual analogue scale)
Patient's global score of disease activity (visual analogue scale)
Physical examination
Number of swollen joints
Number of tender joints
Degree of swelling and/or tenderness
Extraarticular disease:
Minor: nodules, episclertis, pure sensory neuropathy, pleruropericardial disease
Major: vasculitis, Felty syndrome, motor neuropathy, interstitial lung disease
Laboratory
Elevated erythrocyte sedimentation rate (ESR)
Increased C-reactive protein (CRP)
Anemia (in the absence of chronic blood loss or hematuria)
Leukocytosis
Thrombocytosis
Abnormal liver function tests (low albumin, raised alkaline phosphate) in the absence of drug toxicity or liver disease
Inflammatory joint fluid (high polymorph count, low complement, fibrin)
Imaging
Low bone mineral density (juxtaarticular, vertebrae, pelvis) in absence of glucocorticoid therapy or known cause

Graphic 76890 Version 4.0